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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Michael A. Zeligs	Confirmation No.:	9606
Serial No.:	10/616,477	Art Unit:	1618
Filed:	July 9, 2003	Examiner:	Ebrahim, Nabila G
For:	Phytochemicals for the Treatment of Mastalgia, Endometriosis and HPV-related Conditions Including Cervical Dysplasia	Attorney Docket No:	9439-015-999

DECLARATION OF MICHAEL A. ZELIGS UNDER 37 C.F.R. 1.131

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Michael A. Zeligs, do declare and state that:

1. I am a citizen of the United States residing at 568 Rembrandt Road, Boulder, Colorado 80302.

2. I earned a Master's degree in Physiology, Graduate School of Biology, University of California, Santa Barbara, California, in 1972, and a M.D. from the College of Medicine, University of California, Irvine in 1977. I have completed specialty medical training in Anesthesiology, Pediatrics, and Molecular Immunology. As a physician-investigator, I have studied hormonal influences on health beginning with clinical uses of dehydroepiandrosterone (DHEA) in the 1980's. In the 1990's, I began to study estrogen-related disorders, including breast disorders, endometriosis, and cervical dysplasia. I am founder of the company BIORESPONSE, LLC.

3. I am the inventor of the invention described and claimed in the above-identified patent application, Serial No. 10/616,477 (the "'477 application"). The invention relates to methods of treating cervical dysplasia in a subject by administering a dietary indole, *e.g.*, 3,3'-Diindolylmethane ("DIM") and 2-(Indo-1,3-ylmethyl)-3,3'-Diindolylmethane ("LTr-1").

PIEDMONT MEDICAL LABORATORY

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Patient Name:	Address	Birth Date	Age	Sex	Medical Record #
HEITCHEW, VALERIE	484 BATTLEFIELD BLVD NEW MARKET, VA	12/15/54	43Y	Female	

Referring Physician:	Account #:	Room #:	Accession #:	
STAUFFER, JOHN, M.D. New Market Family Practice P.O. BOX 150 New Market, VA 22844		REF LAB	98-13711P	Date Collected: 07/06/98 Date Received: 07/06/98 Date Completed: 07/08/98

ABNORMAL CYTOLOGY

LMP : 06/29/98 FIRST HALF OF CYCLE
SPECIMEN : CERVICAL-VAGINAL PAP
CLINICAL HX: HX ATYPICAL ENDO CERV CELLS

PRIOR CYTOLOGY: 06/25/97 Atypical endocervical cells

SPECIMEN ADEQUACY:
Endocervical component present.

HORMONAL EVALUATION:
Moderate estrogen effect.

DESCRIPTIVE DIAGNOSIS:
Low grade squamous intraepithelial lesion.

* CIN I

RECOMMENDATIONS/GENERAL COMMENTS:
Recommend close interval cytologic followup and/or colposcopic exam.

Kelly Domson, M.D.

appt c Sedlak/Ammann
re: abn pap ? colposcopy

SHENANDOAH VALLEY PATHOLOGY LABORATORIES, INC.
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Seminars in Surgical Oncology 1999; 16:217–221

The Bethesda System and Evaluation of Abnormal Pap Smears

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The Bethesda Pap Smear system and its 1991 revisions aim to simplify Papanicolaou (Pap) smear reporting and make it more reproducible. It redefines the Pap smear request as a medical consultation. The pathologist consultant is required not only to provide the smear reading but also its clinical recommendation. The Bethesda system insists on a detailed Pap smear report assessing specimen adequacy and types of epithelial changes. Squamous cell abnormalities are grouped according to their biologic potential. Both cervical intraepithelial neoplasia, grade I (CIN I) (mild dysplasia) and human papillomavirus (HPV) lesions are grouped together as low-grade squamous intraepithelial lesions (LGSIL), while moderate and severe dysplasia (CIN II and III) belong to the high-grade squamous intraepithelial lesion (HGSIL) category. Atypical squamous cells of undetermined significance (ASCUS) and atypical glandular cells of undetermined significance (AGCUS) need further qualification as to whether they favor either a reactive or neoplastic process. Guidelines for management of abnormal Pap smears are discussed in detail. ***Semin. Surg. Oncol. 16:217–221, 1999.*** © 1999 Wiley-Liss, Inc.

KEY WORDS: **vaginal smears; cervix neoplasms; cervical dysplasia; cervical intraepithelial neoplasia; squamous cell carcinoma; pre-cancerous conditions; cervix uteri; neoplasm staging; tumor virus infections; human papillomavirus; colposcopy; biopsy; risk factors; age factors; predictive value of tests; sensitivity and specificity; false negative reactions; false positive reactions; incidence**

INTRODUCTION

Since the introduction of Papanicolaou (Pap) smear screening 50 years ago, the incidence and mortality rate of cervical cancer in the United States has steadily declined [1]. For 1999, the American Cancer Society (ACS) estimates 12,800 new cases of cervical cancer and 4,800 deaths [2]. It is known that most squamous cell cervical cancers progress through a series of well-defined pre-cancerous lesions that can be detected easily by Pap smear screening. During this pre-invasive stage, squamous intraepithelial lesions or cervical dysplasia can be treated with uniform success.

Since 1988, the ACS and the National Cancer Institute (NCI) have recommended that a Pap smear and pelvic examination should be performed annually after the onset of sexual activity or at the age of 18. After three consecutive negative results, the screening frequency may be decreased at the discretion of the physician and patient [1]. There is still a predominant belief among patients and primary care physicians that older patients do not need a Pap smear. From the National Health Interview Survey in 1992, half of women 60 years and older did not have a Pap smear within the preceding 3 years [1]. More importantly, these women accounted for 25% of new cervical cancer cases and 41% of the disease mortality [1]. This indicates that at diagnosis more of them were found to have advanced disease. Thus, women over the age of 60 should continue to have annual Pap smear screening.

In 1995, the American College of Obstetricians and Gynecologists stressed that those women with risk factors such as history of human immunodeficiency virus (HIV), human papillomavirus (HPV) infection, cervical dysplasia, and multiple sexual partners should have annual Pap smear screening [1].

PAP SMEAR CLASSIFICATION

The traditional Pap smear classification system used numerical designations: class I (for normal), class II (for atypical cells), class III (for cervical dysplasia), class IV (for carcinoma in situ), and class V (for invasive cancer) [3]. A

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major problem with this old system was the lack of standardized cytologic criteria for Pap smear diagnosis, which resulted in high interobserver variation. In 1972, the cervical intraepithelial neoplasia (CIN) system was proposed: CIN I or mild dysplasia, CIN II or moderate dysplasia, and CIN III or severe dysplasia and carcinoma in situ.

In 1988, the NCI sponsored a workshop to standardize Pap smear reporting [3]. Under the new Bethesda system (TBS), Pap smear requests were defined as a medical consultation for the first time [3]. This meant that the requesting doctor has an obligation to provide accurate information to aid in Pap smear interpretation, and the pathologist, in turn, has an obligation to interpret the slide and provide treatment recommendations.

Further, TBS attempts to simplify by classifying a lesion according to its biologic significance. TBS introduces the term "squamous intraepithelial lesion" (SIL) to designate a pre-cancerous lesion. It is further subdivided into high- and low-grade SIL. Included in the low-grade SIL (LGSIL) category are mild dysplasia (CIN I) and lesions suggestive of HPV infection. High-grade SIL (HGSIL) comprises moderate and severe dysplasia (CIN II–III), and carcinoma in situ (CIS) [3].

In 1991, a second workshop was organized to revise TBS (Table I) [3]. Specific criteria were set forth for each cytologic diagnosis as well as the requirement of a statement on the adequacy of a cytologic specimen. The adequacy of specimen can be reported as "satisfactory for evaluation," "satisfactory for evaluation but limited by...," or "unsatisfactory for evaluation due to...." An "unsatisfactory for evaluation" smear should be repeated with a cytobrush to ensure adequate endocervical sampling. All diagnoses with atypical squamous cells of undetermined significance (ASCUS) should be further qualified as favoring a reactive or neoplastic process. To further increase uniformity of Pap smear reporting, an atlas illustrating various cytologic abnormalities and inclusion criteria was also published.

TABLE I. The 1991 Bethesda Pap Smear System*

- Specimen adequacy
  - Satisfactory for evaluation
  - Satisfactory for evaluation but limited to...
  - Unsatisfactory for evaluation due to...
- General categorization (optional)
  - Within normal limits
  - Benign cellular changes
  - Epithelial cell abnormality
- Descriptive diagnoses
  - Benign cellular changes associated with infection: specify trichomonas vaginalis, fungal organisms consistent with *Candida*; predominance of coccobacilli consistent with shift in vaginal flora; bacterial consistent with *Actinomyces*; cellular changes associated with herpes simples virus; or others
  - Reactive cellular changes associated with inflammation and cellular repair; atrophy with inflammation (atrophic vaginitis); radiation; intrauterine device, or others (specify)
- Epithelial cell abnormalities
  - Squamous cell abnormalities
    - Atypical squamous cells of undetermined sifnigicant (ASCUS) favoring neoplastic or reactive process (specify)
    - Low-grade squamous intraepithelial lesion (LGSIL) consistent with human papillomavirus (HPV) infection or mild dysplasia (CIN I)
    - High-grade squamous intraepithelial lesion (HGSIL) consistent with moderate and severe dysplasia (CIN II–III), carcinoma in situ (CIS)
  - Squamous cell carcinoma
- Glandular cell abnormalities
    - Atypical glandular cells of undeteremined significance (AGCUS) favoring neoplastic or reactive process (specify)
    - Endometrial cells present
    - Endocervical adenocarcinoma
    - Endometrial adenocarcinoma
    - Extra-uterine or unspecified adenocarcinoma
- Hormonal evaluation (for vaginal smear only)
  - Hormonal pattern compatible with age and history
  - Hormonal pattern incompatible with age and history
  - Hormonal evaluation not possible due to...

*Modified from [1].

GUIDELINES FOR ABNORMAL PAP SMEARS

In 1992, the NCI organized another workshop to devise management guidelines for abnormal Pap smears [3].

Unsatisfactory Smears

In a survey of different laboratories, it was discovered that scant cellularity contributed to 70% of unsatisfactory smears, and obscuring inflammation contributed to 28% [3]. Among those in the category of "satisfactory but limited by..." 60% of unsatisfactory smears were due to lack of endocervical cells and another 28% to obscuring inflammation. Kost et al. examined the "less than optimal" smears and compared them to the dysplasia pickup rate in repeat smears [4]. They found that repeat Pap smear is a low-yield procedure in this category and that lack of endocervical cells should not be the sole criterion for repeat Pap smear. The NCI defers this decision to the clinician's judgment of the patient's risk and her need for a repeat Pap smear.

Atypical Squamous Cells of Undetermined Significance (ASCUS)

Some squamous cell abnormalities are more abnormal than those seen with reparative or inflammatory change, but are not severe enough to qualify for dysplasia. They do not correspond to the traditional class II Pap smear, or cellular atypia, or inflammatory atypia, and because of unknown significance, they are termed ASCUS. Approximately 5% of Pap smear reports are ASCUS, and in most laboratories, the ASCUS rate should be no more than two to three times higher than that of LGSIL [3]. After careful review of all ASCUS smears, the most common final diagnoses are squamous metaplasia and HPV lesions. In 1994, Widra et al. studied a group of 124 patients with

ASCUS [5]. They found 5% of ASCUS smears with CIN II–III on colposcopically directed biopsies—and that only smears favored as neoplasia had these pre-cancerous lesions. Because the qualification method of ASCUS (favoring a reactive or neoplastic process) had 100% sensitivity and negative predictive value, they recommended that colposcopy should be reserved for patients with ASCUS smears favoring neoplastic process. Montz et al. studied 632 women with abnormal smears followed by repeat Pap and colposcopy every 3 months [6]. After 9 months, 46.2% of ASCUS smears had persistent change, none had progression, and 53.8% had spontaneous regression. Slawson et al. examined 159 women with ASCUS and found CIN II–III in 9.4% of smears [7]. Similarly, Taylor et al. found CIN II–III in 6% of ASCUS smears, HPV changes in 11% and LGSIL in another 17% [8]. In 1996, Kaufman reported finding CIN II–III in 9% and CIN I in another 8% of ASCUS smears [9]. Thus, cervical dysplasia can be found in 5% to 20% of ASCUS cases, especially in those favoring neoplastic process.

Management Options for ASCUS

Repeat Pap smears without colposcopy is an acceptable option for an unqualified ASCUS diagnosis or one favoring a reactive process. Repeat Pap should be performed every 4 to 6 months for 2 years until there are three documented consecutive negative smears. The follow-up smears should be qualified as "satisfactory for evaluation." For non-compliant patients and those with repeat ASCUS, colposcopy should be done. Patients with severe inflammatory exudates should have the infection identified and treated, whether it is chlamydia, gonococcal cervicitis, trichomonas, candida vaginitis, or bacterial vaginosis. Treatment with various antibiotic creams in the absence of a specific diagnosis is not indicated.

Post-menopausal women with ASCUS Pap smear who are not taking hormones should be treated with topical estrogens and have the smear repeated in 2 months. If persistent ASCUS is found, colposcopy should be offered. If the ASCUS diagnosis is favored with a neoplastic process, colposcopy is warranted. In addition, colposcopy should be considered for the high-risk patients such as those with history of abnormal smears, poor compliance, and HIV or HPV infection.

Low-Grade Squamous Intraepithelial Lesions (LGSIL)

Approximately 5% to 40% of LGSIL Pap smears are associated with CIN II–III. Rarely is there an underlying carcinoma. In a large study of LGSIL Paps followed by repeat Pap and colposcopy for 9 months, 18.2% persisted, 3.4% progressed, and 78.3% regressed [6]. The authors concluded that a majority of women with confirmed minimal cytologic change on Pap smear have complete colposcopic and cytologic regression. Because of the 60% to 78% spontaneous regression rate, some authors have advocated conservative treatment with repeat Pap smears [6]. Subsequently, Wright et al. applied this approach and reported 74% sensitivity and 67% specificity of repeat Pap in detecting biopsy-proven dysplasia in a group of 398 women with ASCUS or LGSIL [10,11]. Thus, one needs to remain cautious that repeat Pap can miss a significant number of lesions.

Alternatively, Flannelly et al. advised colposcopy on all LGSIL patients as a more cost-effective approach because they found that 70% of them eventually required colposcopy anyway and a significant number had biopsy-proven severe dysplasia [12].

Management Options for LGSIL

An established method for following reliable patients with LGSIL is to repeat the Pap smear every 4 to 6 months for 2 years. If a repeat Pap shows persistent abnormality, colposcopy is indicated. After three consecutive Pap smears have proven negative, patients can resume annual follow-up. (It has been determined that a patients needs three consecutive negative Pap smears to reduce to 3% the risk of missing a high-grade lesion [13].) Colposcopy with directed biopsy and endocervical curettage is another acceptable management option. Tissues should be obtained in the least traumatic way to confirm the lesion on histology. Routine loop electrosurgical excision (LEEP) of the transformational zone and normal-appearing cervix is not recommended as an initial method of evaluating ASCUS or LGSIL smears because of the high rate of normal histology. Following biopsy confirmation of LGSIL, the lesion can be excised, frozen, cauterized, vaporized, or followed conservatively if the entire lesion as well as the transformational zone can be visualized. However, surgical excision or ablation is strongly advised for non-compliant patients and those who wish definitive therapy. Surgical ablation with histologic confirmation is inappropriate and unacceptable. If the entire lesion is not seen, cervical conization is indicated.

High-Grade Squamous Intraepithelial Lesions (HGSIL)

Patients with HGSIL smears should undergo colposcopy and directed biopsy. After histologic confirmation—and if the entire lesion and transformational zone can be visualized—either excisional or ablative therapy is indicated to remove or destroy the entire lesion and the transformational zone. If the entire lesion or the transformational zone cannot be seen, a cone biopsy is indicated. In pregnant women, diagnostic and treatment options should be delayed until post-partum unless invasive carcinoma is suspected. Cervical conization is rarely indicated during pregnancy.

Atypical Glandular Cells of Undetermined Significance (AGCUS)

Glandular cells with abnormalities more severe than changes of a reactive or inflammatory process but not severe enough to qualify for neoplasia are called atypical glandular cells of undetermined significance or AGCUS [14,15]. This category includes atypical endometrial-like cells, atypical endocervical-like cells, and atypical glandular cells of unknown origin. These cells may originate from endocervix, endometrium, Fallopian tubes, or ovaries. Since abnormal glandular cells can originate high in the canal, complete evaluation should include Pap smear with cytobrush, endocervical, and endometrial samplings. Similar to ASCUS, atypical glandular cells should be qualified as favoring a reactive or neoplastic process. The minimum workup for AGCUS is colposcopy, biopsy, and endocervical curettage (ECC). If AGCUS smears show cells originate from the endometrium or unknown origin, pelvic ultrasound and endometrial biopsy (EMB) should be done. Approximately 20% to 50% of AGCUS smears have underlying high-grade CIN. Those favoring a neoplastic process should undergo immediate colposcopic examination and directed biopsy with ECC and EMB. In the Cleveland Clinic series, Kennedy et al. found an AGCUS Pap rate of 0.2% [16]. Further evaluation helped uncover cervical adenocarcinoma in 10%, cervical dysplasia in 5% and endometrial cancer in another 1%.

The management options for an AGCUS smear favoring a reactive process is still unclear. If the smear is suspicious for adenocarcinoma in situ, a cone biopsy should be done. Patients with persistent AGCUS and those not reconciled by the above diagnostic modalities should have a cone biopsy and dilatation and curettage (D&C).

CONCLUSIONS

The current Bethesda Pap smear system has 85% sensitivity and 90% to 99% specificity in detecting cervical dysplasia [17]. Its false-negative rate is estimated to be 20% [1]. The majority of false-negative results come from sampling error (60%) and screening error (40%). Interpretation rate is rare. Physicians can reduce sampling error by careful techniques to make sure that both endocervical canal and ectocervix are sampled. False-positive results may be due to interpretive error, cervicitis, reparative changes, radiation, chemotherapy, or squamous metaplasia [17]. The ThinPrep is being popularized as a liquid-based collection system with potential improvements [1]. However, a recent study failed to show any significant advantage over the conventional Pap smear system [18]. In 1995, the U.S. Food and Drug Administration approved PapNet, a computer-based Pap smear reading system. Its primary use is to rescreen equivocal or atypical Pap smears [19], and it also is an excellent tool for quality control assessment in various laboratories.

Since the conversion to the Bethesda system, it appears that the new Pap smear system may create more confusion than it eliminates. During the past decade, the cost and morbidity associated with the detection and treatment of low-grade cervical lesions has escalated with questionable benefits. Out of 50 million Pap smears performed annually in the U.S., it has been estimated that approximately 2.5 million have low-grade abnormalities, for which the optimal management remains controversial [3]. The cost to evaluate and treat these low-grade lesions is nearly 6 billion dollars, and again, the benefits are questionable. The problem has been complicated further by the introduction of new technologies such as LEEP, microcolposcopy and HPV typing [11,20].

Several critics have voiced the concern that TBS may result in over-diagnosis and unnecessary treatment [21]. Since HPV changes are now grouped together with LGSIL, the concern is that some practitioners may now consider koilocytotic atypia as neoplastic and treat it. In addition, even though moderate dysplasia is grouped together with HGSIL, a significant portion of this lesion will regress spontaneously. On the other hand, conservative treatment with repeat Pap smear can miss a significant number of lesions. When Slawson et al. followed 122 women with colposcopy for cervical atypia, a single Pap smear alone failed to detect one-third of biopsy-proven high-grade lesions (CIN II–III) [7]. They discovered that the detection rate improved to 93% when a combination of repeat Pap and acetic acid staining was used.

Since the advent of LEEP, several authors have popularized the concept of "see and treat" with LEEP during the same visit. In 1994, Higgins et al. evaluated the various modalities including repeat Pap, colposcopy, and "see and treat" with LEEP in 214 patients with abnormal Pap smears [13]. They concluded that patients with an initial Pap smear showing ASCUS or LGSIL would benefit from repeat Pap smear for colposcopically directed biopsy before definitive treatments because a high proportion of them have normal histology. In contrast, patients with a colposcopic impression of high-grade dysplasia combined with HGSIL on Pap smear can undergo immediate loop excision.

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Kathleen Ammann, M.D.
Kelly Dowson, M.D.

Patient Name:	Address:	Birth Date:	Sex:	Medical Record #:
HEFTCHEW, VALERIE	484 BATTLEFIELD BLUFF DR NEW MARKET, VA	11/15/1954 44 years	F	

Referring Physician:	Account #:	Room #:	Accession #:	
STAUFFER, JOHN, M.D. New Market Family Practice P.O. Box 250 New Market, VA 22844		reF LAB	P99-012837	Date Collected: 08/03/1999 Date Received: 08/03/1999 Date Completed: 08/17/1999

ABNORMAL GYN CYTOLOGY

LMP: 07/28/1999 First Half of Cycle
SPECIMEN: Cervical-Vaginal
CLINICAL HX: ABN YES 070698 HORMONES

PRIOR CYTOLOGY:

Smear Quality
Endocervical component present.

Additional Findings
Endometrial cells present.

Hormonal Evaluation
Moderate estrogen effect.

DESCRIPTIVE DIAGNOSIS:
Atypical squamous cells of undetermined significance.

Recommendation/General Comments:

ATYPICAL METAPLASTIC CELLS/FAVOR REACTIVE

ELECTRONIC SIGNATURE ON FILE
Kathleen Ammann, M.D.

AFTER DIM

The Pap smear is a cancer screening test that has an overall 15-25% false negative rate.
For this reason, *an annual Pap smear is recommended.* Please discuss this with your patients

Referred by Piedmont Medical Laboratory